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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,280	03/10/2004	Michele Cargill	CL1510ORD	9662

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CELERA, AN APPLERA BUSINESS UNIT
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EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,280	CARGILL ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 30 October 2007.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,6 and 25-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,6 and 25-37 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007 has been entered.
2. This action is in response to the papers filed October 30, 2007. Currently, claims 1, 6, 25-37 are pending.
3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
4. Any objections and rejections not reiterated below are hereby withdrawn.
 - a. The 103 rejection has been withdrawn in view of the cancellation of Claims 21-22.
 - b. The new matter rejection after further consideration has been withdrawn.

Maintained Rejections

Priority

5. This application claims priority to provisional applications 60/453,050 filed March 10, 2003 and 60/466437, filed April 30, 2003.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 6, 25-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 6, 25-37 are drawn to a method for identifying a human who has an altered risk for developing coronary stenosis by detecting a SNP at position 101 in SEQ ID NO: 19350 in said humans nucleic acids wherein the presence of an A at position 101 indicates a decreased risk of developing coronary stenosis and the presence of a G indicates an increased risk of developing coronary stenosis.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches polymorphisms in Apolipoproteins which are not associated with severe aortic valve stenosis. APOA, AK38, plasminogen gene are all synonyms of LPA which the instant polymorphisms lies within. Avakian et al. (Clinical Genetics, Vol. 60, pages 381-384, 2001) teaches a G/A polymorphism APO A1 which is not significantly associated with AS (see Table 3). Thus, it is clear that not all polymorphisms in the gene APO A1 is associated with each stenosis.

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn et al. suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-

environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer *et al.* (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpk15 and cadpk16 are not associated with the disease, however cadpk17 has a p-value of less than 0.05, and therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that any polymorphisms within SEQ ID NO: 19,350 is associated with any risk for any stenosis in any individual.

The specification does not provide guidance for any altered risk for the SNP at position 101 of 19,350. The specification teaches hCV2590271, SEQ ID NO: 19,350 was analyzed in S0012 and V0002 samples. As seen in Table 7, page 5, the hCV25930271 is not significantly associated with coronary stenosis in the second population (p-value 0.41193). It is thus unpredictable whether the SNP is predictably associated with stenosis given the unpredictable association in two different stenosis populations. The specification teaches there is an association between the SNP and coronary stenosis in population 1. However, it is unpredictable given the varying statistical data provided in the specification whether the skilled artisan could make and use the instant invention without further unpredictable and undue experimentation.

Neither the specification nor the responses specifically address the concept of heterozygote individuals and homozygosity. The Table 7 merely states the frequencies of T allele. The specification appears to teach that the presence of a T allele is significantly associated in population S0012, but not in population V0002. The detection of a T or complementary A allele would thus encompass both heterozygotes and homozygotes with either an AA or AG. Thus, the mere detection of a G or complementary C allele at position 101 would not necessarily indicate an increased risk of coronary stenosis since the specification appears to include these individuals in the analysis of the A allele. If a person is a heterozygote with a GA genotype, it is unclear how the person may be at both an increased and a decreased risk for coronary stenosis.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, it is unpredictable any polymorphisms is associated with altered risk any stenosis in any individual. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response submits additional studies published earlier this year showing the LPA I4399M SNP is associated with Severe Coronary Artery disease in three different samples. This argument has been considered but is not convincing.

As previously stated and as provided in MPEP 716.02(g), evidence of publications post filing is not acceptable absent presentation in declaration form. Specifically, "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. *Ex parte Gray*, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). Publications may, however, be evidence of the facts in issue and should be considered to the extent that they are probative. Here, the post-filing experiments are not in declaration form.

With further respect to the post-filing date paper, not in declaration form, Luke teaches the LPA I4399M SNP is associated with severe CAD. The instant claims are drawn to coronary stenosis. Applicants are requested to discuss the relationship between CAD and coronary stenosis. In the event that the two terms are not synonymous, the post-filing date paper would not appear to corroborate the findings in the specification.

The response does not address the herterozygosity issue and how the presence of a G indicates an increased risk and the presence of an A indicates a decreased risk.

Applicants are reminded of MPEP 705.09 and 716.01 for the seasonal presentation of affidavits.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

8. No claims allowable.

9. This is a RCE of applicant's earlier Application No. 10/796,280. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.



J. Goldberg

Jeanine Goldberg

Primary Examiner

January 23, 2008